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74. The plant cell of claim 71 wherein said immunoglobulin heavy chain variable region is a full length variable region.

75. The plant cell of claim 71 wherein said nucleotide sequence also encodes at least a portion of the constant region of an immunoglobulin heavy chain.

76. A plant comprising the plant cell of claim 53.

REMARKS

The present invention stems from Applicants pioneering discovery that single immunoglobulin polypeptides and fully assembled antigen-specific immunoglobulin can be produced in a plant cell. Plant produced antibodies are useful for systemic protection through administration i.v. as well as localized protection through local administration to a mucosal surface (e.g., lungs, digestive tract, nasopharyngeal cavity, the urogenital system).

After amending the claims as set forth above, claims 53-65 and 67, 68, and 70-76 will be pending in this application. The amendments and the new claims find ample basis in the application as filed and, therefore, raise no issue of new matter. For example, support for "antigen-specific immunoglobulin" is found, for example, at page 10, line 27-33 (emphasis added):

> Immunoglobulin product: A polypeptide, protein or multimeric protein **containing at least the immunologically active portion of an immunoglobulin heavy chain and is thus capable of specifically combining with an antigen**. Exemplary immunoglobulin products are an immunoglobulin heavy chain, immunoglobulin molecules, substantially intact immunoglobulin molecules, **any portion of an immunoglobulin** that contains the paratope, including those portions known in the art as Fab fragments, Fab' fragment, $F(ab')_2$ fragment and Fv fragment.

Reference in the above quote to "at least the immunologically active portion" . . . any portion of an immunoglobulin . . . including those portions known in the art" is broad language strongly demonstrating that any and all fragments were contemplated. This

would include nearly complete heavy and/or light chain with only one or a few amino acids removed to deletion mutants lacking particular segments or domains (e.g., a constant region domain). This view is additionally supported by page 3, lines 1-6 (emphasis added) of the specification.

> One of the most useful aspects of using a recombinant expression system for antibody production is the ease with which the antibody can be tailored by molecular engineering. **This allows the production of antibody fragments and single-chain molecules, as well as the manipulation of full-length antibodies.** For example, a side [sic] range of functional recombinant-antibody fragments, such as Fab, F_v, single-chain and single-domain antibodies, may be generated.

This passage indicates that recombinant expression makes possible the production of a variety of antigen-specific immunoglobulins including those known from proteolytic processing (e.g., Fab) and those known only by recombinant expression of light and heavy chain variable regions (e.g., single chain antibodies).

The ordinary skilled artisan would have appreciated that recombinant DNA methods can be used to produce any of a variety of antibody fragments and not just those known previously by proteolytic cleavage . This is evidenced by the state of the art as of the earliest filing date of the instant application. For example, U.S. Patent no. 4,816,567 to Cabilly et al., filed April 8, 1983, describes the use of recombinant DNA technology to express antibodies that have less than a full length heavy or light chain (Summary of the Invention; emphasis added).

> The invention relates to antibodies and to non-specific immunoglobulins (NSIs) formed by recombinant techniques using suitable host cell cultures. . . .
>
> Finally, either the light chain or heavy chain alone, **or portions thereof**, produced by recombinant techniques are included in the invention and may be mammalian or chimeric.

Cabilly also teaches recombinant expression of any and all immunologically active fragments by referring to expressing "at least the variable domain" of light and heavy chains.

U.S. Patent No. 4,704,692 to Ladner (cited on page 28 lines 5-13 of the instant application) teaches that recombinant methods can be used to express unique fragments of immunoglobulins in which terminal amino acids at the N- or C-terminus of the variable region of light or heavy chains are removed as part of the strategy for linking the chains with a peptide linker to form a single chain Fv fragment. Such antibody fragments would be immunologically active while comprising less than a full length variable domain and no constant domains.

Schwartzbaum et al. (Eur. J. Immunol., vol. 19(60, 1015-1023; 1989; attached as Exhibit A) used molecular biology techniques to construct IgE antibodies with deletions in either the $C_\epsilon 4$ and $C_\epsilon 3$ constants domains (see abstract). Similarly, Bettler et al. (PNAS, 86:7118-7122, 1989; attached as Exhibit B) describes preparation of a large number of IgE constant domain deletion mutants involving a fragment comprising less than the heavy chain constant region (see Fig. 2).

Thus, it is respectfully submitted that the phrase "portion thereof" raises no issue of new matter.

FORMAL DRAWINGS

Formal drawings will be submitted under separate cover.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The rejection of claims 53-66 as allegedly lacking a written description is respectfully traversed. Applicants refer the Examiner to arguments made in the Amendment filed March 18, 2002.

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REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The rejection of claims 53 has 55 for allegedly lacking clarity under 35 USC § 112, second paragraph is respectfully traversed. Applicants refer the Examiner to arguments made in the Amendment filed March 18, 2002.

REJECTION UNDER 35 U.S.C. § 102 OVER DÜRING

The rejection of claims 53-56 and 58-63 under 35 U.S.C. § 102(b) as being allegedly anticipated by During (Dissertation) is respectfully traversed. Applicants refer the Examiner to arguments made in the Amendment filed March 18, 2002.

REJECTION UNDER 35 U.S.C. § 103 OVER DÜRING

The rejection of claims 53-66 under 35 U.S.C. § 103(a) as being allegedly obvious over During is respectfully traversed. Applicants refer the Examiner to arguments made in the Amendment filed March 18, 2002.

REJECTION OVER GOODMAN

Although the claims have not been rejected over U.S. Patent No. 4,956,282 to Goodman, this question was raised during the recent interview. Applicants will discuss the Goodman reference and explain why it does not anticipate or otherwise render obvious the claimed invention.

First, it is noted that Goodman makes only a passing reference in a single paragraph to expressing immunoglobulin heavy and light chains together in plant cells. Except for this gratuitous statement, the reference is other wholly devoid of teaching for expressing an immunoglobulin in plant cells. Goodman does not even consider the possibility that light chains may be expressed by themselves and that such chains can be produced in a manner that allows them to form an antigen specific immunoglobulin when co-expressed in plant cells with the corresponding heavy chain.

Goodman's success with gamma interferon is of no significance to the claimed invention because although gamma interferon is a single polypeptide, it is naturally a single polypeptide. Expressing a natural single polypeptide does not predict whether or not one can express a single polypeptide that naturally is expressed as a heterodimer. The light chain is naturally expressed as a member of a heterodimer (the Ig molecule) so the teachings related to interferon, a natural single polypeptide, are not relevant to expressing an immunoglobulin light chain. Accordingly, in view of the above and prior arguments of record, it is respectfully submitted that the claims are not anticipated or obvious over Goodman.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is urged to contact the undersigned by telephone to address any outstanding issues standing in the way of an allowance.

Respectfully submitted,

Date: May 31, 2002

By _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

53. (Amended twice) A plant cell containing:

(a) nucleotide sequence encoding an [~~antigen-specific~~] immunoglobulin product comprising at least a portion of the variable region of an immunoglobulin light chain and a leader sequence forming a secretion signal, **said light chain derived from an antigen-specific immunoglobulin comprising a heavy and light chain** and;

(b) [~~antigen-specific~~] immunoglobulin product encoded by said nucleotide sequences wherein said leader sequence is cleaved from said immunoglobulin light chain following proteolytic processing, said light polypeptide product being capable of forming an antigen-specific immunoglobulin when co-expressed in the same cell with said heavy chain from said antigen-specific immunoglobulin.

54. (Amended) The plant cell of claim [~~53~~]**55** wherein the immunoglobulin product is a single-chain antigen-binding protein.

55. (Amended twice) The plant cell of claim 53 wherein the immunoglobulin product [~~comprises one heavy chain and one light chain~~] **further comprises at least a portion of the variable region of an immunoglobulin heavy chain**.

57. (Amended) The plant cell of claim [~~53~~]**55** wherein the immunoglobulin product is an abzyme.

58. (Amended twice) The plant cell of claim [~~53~~]**55** wherein the immunoglobulin product comprises a Fab.

59. (Amended twice) The plant cell of claim [~~53~~]**55** wherein the immunoglobulin product comprises a Fab'.

60. (Amended twice) The plant cell of claim [~~53~~]**55** wherein the immunoglobulin product comprises a F(ab')2.

61. (Amended) The plant cell of claim [~~53~~]55 wherein the immunoglobulin product comprises an Fv.

62. (Amended twice) The plant cell of claim [~~53~~]55 wherein the immunoglobulin product comprises a full-sized antibody.

70. (Amended) The plant cell of claim [~~69~~]55 wherein said portion of said heavy chain is from a heavy chain selected from the group consisting of IgG, IgM, IgA, IgD and IgE.